Reviewer's report

Title: Economic evaluation of Type 2 Diabetes Prevention Programmes: Markov model of low- and high-intensity lifestyle programmes and metformin in participants with different categories of intermediate hyperglycaemia

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Reviewer: David Nathan

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Roberts et al. present the results of health economics analyses that use Markov models to determine the costs of diabetes prevention with intensive and low(er) intensity ("pragmatic") lifestyle interventions and metformin to prevent the development of diabetes in high risk groups. They define the "high risk groups" (pre-diabetes or intermediate glycemia) based on IGT, IFG or HbA1c. The authors use a 50-year horizon and base their analyses on a variety of published sources. They conclude that although intensive lifestyle interventions would result in the greatest efficacy, low-intensity lifestyle intervention would be the most cost-effective.

I have little to critique regarding the specific analytic methods, but several concerns regarding the premises.

1) The authors perform analyses based on whether the patients are high-risk based on having IFG, IGT or high-risk A1c (6.0-6.4). The authors refer to "isolated" HbA1c (on page 7 line 13), but it is unclear how the underlying data were analyzed or how these categories are used in the analyses. Of note, the Venn diagram of IFG, IGT and abnormal HbA1c are largely overlapping, i.e. "isolated" categories would be somewhat uncommon, compared with the overlap. Although I agree completely that these measurements reflect different underlying pathophysiology, as the authors note on page 10, line 17, the substantial overlap of abnormal states is nowhere mentioned. The entire premise of the analyses by "pre-diabetes" type is that these states have different outcomes, responses to therapy and costs. The authors make their decisions -apparently- based on the premise that these are isolated states.

2) Similarly, I can't easily find how the development of diabetes is made. For example, if most cases are identified by HbA1c—which is increasingly the case, at least in North America—then those with HbA1c as the basis of the identification of high risk are certainly going to have a greater conversion to diabetes if HbA1c is also used as the means of diagnosis. Similar arguments could be made for IFG and IGT. So, which diagnostic criteria are being used in the modeling?

3) The largest and longest follow-up studies by far are the DaQing, FDPS and US DPP (and DPPOS). The largest of these, DPP, recruited patients with both IGT and elevated fasting glucose and increased BMI. The others used IGT and body mass. The recruitment criteria to the pragmatic lifestyle studies are all over the place, but they are far more brief. If the longest term studies are being used to determine the efficacy of interventions, I can't imagine how the data sustain a 50 year horizon (the DPP is into its ~17-20 year follow-up, with the most recent report capturing 15 year follow-up, and DaQing reported 20 year outcomes, but with very poor direct study.) How can you justify these very-long term projections when the published data on the
longest trials is only 20 years and the lower-intensity studies have usually examined weight loss-rather than diabetes prevention- and usually for ~ 1 year.

4) Similar to number 3 above, the modeling uses 50-59 year olds and a 50 year horizon. The actual studies on which efficacy is based had a much wider range of ages. The effects of therapy in DPP- one of the few studies large enough to examine the effects of age at time of intervention on efficacy- were very much affected by age (for example, metformin more effective in the younger aged population and almost ineffective in those older than 60). The modeling doesn't take this into account.

5) With regard to efficacy, the authors present one of the most important assumptions in a single sentence on page 15, lines 1-5, specifically, the long-term reductions in incidence (provided by the various interventions in the three pre-diabetic groups- FPG,IGT, and A1c). The efficacy of the interventions across the three subgroups is not only unique, but underlies the economic analyses. These data should be highlighted in a table. In addition, the relative risk reductions should be shown in addition to the absolute incidences that are currently provided.

If I understand the data correctly, the table might look like this:

<table>
<thead>
<tr>
<th>Diabetes Incidence over 50 years</th>
<th>Control</th>
<th>Prag</th>
<th>INT Lifestyle</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>42</td>
<td>41</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>FPG</td>
<td>38</td>
<td>37</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>HbA1c</td>
<td>38</td>
<td>37</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

As noted above, I would add the risk reduction.

I will focus on the metformin intervention, since the data source should be the DPP/DPPOS as it is the only study with long-term follow-up with metformin treatment, so the source of the estimates is clear. If the data were given more clearly as risk reduction, the reader could trace the values back to the original study(ies) of origin.

Minor comments
The use of "pragmatic" to describe the lower intensity lifestyle intervention is editorial and should probably be reserved for the discussion. Would be consistent and describe the intervention as Lower Intensity.

In the abstract and introduction, you refer to US (and UK) recommended low intensity interventions. In fact, the largest studies and programs in the US are the DPP intervention. The majority of studies that use less intensive interventions (if the duration of the study is used as a means of classifying them as "low intensity"), were of brief duration because of the desire of investigators to perform short-term (usually 1 year) studies. In general, these studies almost always used the DPP-program (~16 sessions in first 6 months, followed by 4-6 sessions). It is true that the majority used group - as opposed to individual- sessions, but again this needs to be made clear.

Page 6, lines 45-48- entirely redundant- see lines 26-29 above
Page 7, lines 23-25 - again, would be careful in suggesting that the US "favours low intensity lifestyle programs"

Page 9, line 43  HaA1c, typo

Page 11, line 1 - again, the data regarding metformin must be from the DPP/DPPOS and the assumption that the risk reduction is constant "over ten years for the metformin as this is the longest period of followup available..." is inaccurate. The DPPOS has, I believe, published its 15 year data. The risk reduction fell from ~31% at 3 years to 18% by year 10, and then remained stable at year 15.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

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